DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Centers for Disease Control and Prevention
National Institute for Occupational
Safety and Health
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Dear Dr. Jarabek:

This letter is in response to your request to National Institute for Occupational Safety and Health (NIOSH), initially discussed with Dr. Leslie Stayner, for a review of perchlorate health effects studies. The thirteen human epidemiological studies that you provided have been evaluated in the enclosed report.

As you will see, the studies represent rather preliminary efforts using traditional approaches that generally were unable to shed much light on some key issues. Although, for the most part, the studies show that typical clinical manifestations of thyroid disease were not notably elevated in populations with perchlorate-contaminated drinking water, there were serious issues of confounding that made this interpretation difficult. On the other hand, among neonates for whom there are significant neurodevelopmental concerns related to endocrine status, there were some clear indications of altered thyroid responsiveness. The report concludes that the current epidemiological assessments fall short of providing a basis for assigning safe levels of perchlorate contamination with any confidence.

If you have any questions concerning these conclusions or other aspects of this report, please feel free to contact me.

Sincerely yours,

Robert M. Park
Epidemiologist, Risk Evaluation Branch
Education and Information Division

Enclosure

National Institute for Occupational Safety and Health
Education and Information Division - Risk Evaluation Branch
Robert M. Park
November 2, 2001

Perchlorate Health Effects in the Epidemiological Literature

Overview

To be informative, epidemiological studies must pose research questions that are based on appropriate physiological issues. In some contexts, a sufficient specification may take relatively simple form. For example, with occupational cancer, the generally assumed underlying mechanisms lead to a simple test: does exposure to substance(s) X at time t_1 increase the incidence of specific cancers at time $t_2 > t_1 + a$, where $a>0$ is some lag time. The relation of risk at t_2 to the history of prior exposure may be a complex one but almost always risk is an increasing function of $X(t_i)$. This test may require controlling for confounding factors, which is usually not difficult when relevant detailed information is available.

In contrast, the effect of an environment exposure on a regulated system could be more of a challenge. Thus cancers whose risk depends on endocrine status introduce increasing complexity. Environmental perturbations of physiological systems that have inherent variability over time and are imbedded in control networks that function to minimize disruption present the challenge of what end-points to measure. Cross-sectional assessments during chronic exposures will capture regulatory variability on the part of some measures while others will tend to stabilize at "normal" levels despite substantial environmental influences. Short-term fluctuations in exposure are often irrelevant for chronic diseases such as lung cancer or other respiratory diseases but conceivably may be important for endocrine system functions that impact developmental, hyperplastic, immune or autoimmune events.

The effect of the perchlorate anion on the thyroid system is an example of a potentially difficult characterization. Important effects may be evident as shifts in average levels of measurable factors, but more important effects may involve alterations in transient responses to demands on the regulated system. Multiple covariates of potential perchlorate health effects include iodine availability, age, gender, ethnicity, diet and possibly social class. For neonates, the birth process itself stimulates an endocrine cascade with the amplitudes of end-point variation depending on birth weight, gestational age, age at sampling (in hours), and possibly environmental temperature. Post partum developmental risk factors would include perchlorate exposure via lactation. Individual perchlorate exposure is difficult to measure or even estimate in population-based studies.

Comments on Specific Studies

1. Occupational Exposures

There are two publications investigating workers in ammonium perchlorate production.[1,2] These studies were cross-sectional in design and therefore subject to survivor bias in that workers experiencing adverse effects could have left employment. This issue was not addressed. It would have been particularly noteworthy had any absent former employee experienced thyroid disorders, aplastic anemia or related hematological disorders, which have been reported in settings where perchlorate is used for short periods at higher doses as a therapeutic agent.[3] The airborne exposures that were characterized corresponded to daily doses on the order of 20-50 mg and possibly higher as the air-sampling methods excluded large particulate (> 50 μm) that could add considerable mass to the daily inhaled or ingested dose. (In the study that investigated this, the daily absorbed dose, based on urinary perchlorate, *exceeded* the inhaled dose[2] [Fig. 5].)

In the study of Gibbs et al.,[1] there were indications of perturbed thyroid function but none was statistically significant. TSH increased by 10% across a single work shift in an exposed group (n=18) compared to an unexposed group (n=83), groups that together comprised less than half of employees eligible for study. Comparison of workers in three groups (unexposed, low and high cumulative exposure) resulted in consistent patterns for all thyroid parameters in which the unexposed group had values intermediate between those of the low and the high cumulative dose groups. This suggests that important confounding was present – i.e., that the comparison group, which apparently included office workers, differed from the exposed groups on other important risk factors as well [Table 5]. For thyroid (TSH) and liver outcomes (SGOT, GGPT, SGPT), there were subtle indications of exposure effects: the standard deviation increased substantially in the high dose group, as did the average values but not the percentiles up to the 75th, suggesting that a small subgroup had undergone a considerable upward excursion [Tables 5, 6]. Statistical tests (regression analysis) of these effects were severely limited by the apparent confounding that affected baseline levels.

The second study of ammonium perchlorate workers, by Lamm et al.,[2] assembled a comparison group at the same facility from an unrelated process thought to have low exposure to perchlorate. Surprisingly, the comparison group had current absorbed doses equal to 20% of the low perchlorate-exposed group and 3% of the high exposed group even though the inhaled dose of the comparison group was 4% of that of the low dose and 0.02% of the high dose group [Tables1, 2]. This suggests that there was considerable exposure misclassification, arising perhaps from general environmental contamination at the work site or in clothing. In one subject, urinary perchlorate increased over a 12 hr period during which there was thought to be no exposure [Fig. 2]. No

significant associations were observed between perchlorate exposure and thyroid parameters; however, measures of cumulative exposure were not considered. Suggestions of increasing trends for T_3, T_4 and maximum-T_3 were not statistically significant but were based on small numbers (nos. of workers in exposure groups: 21 (unexposed), 13, 8, 15) [Table 3].

In these two cross-sectional occupational studies, there was no clear evidence for any perchlorate effect on thyroid function. However, historical exposure classification was limited in one study and absent in the other. Former employees were lost to followup, and neither study controlled for potential confounding arising from body mass, environmental temperatures, or socioeconomic status. There was no measurement of thyroid iodine reserve or thyroid dynamic responsiveness that conceivably could be altered even though steady-state TSH and T_4 levels appear to be in the normal range.

2. General Population Studies

Just four published studies have examined thyroid-effects related to perchlorate in the general population,[4-7] including one in children[5] and two in experimental adult subjects.[6,7]

Li et al. investigated medical claims for thyroid problems in a Medicaid insured population in Nevada, comparing all counties that were known not to have perchlorate contaminated drinking water with the one county that did (approx. 10 μg/L).[4] This was a study of *period-prevalence* (proportion of population that had claims for thyroid-related disorders any time during a two-year period); incident cases could not be identified within this database. Eight distinct disorders were analyzed including two with very low prevalence: congenital hypothyroidism (0.01%) and thyroid cancer (0.02%). Comparisons were made between the exposed county, which includes Las Vegas, and a) an unexposed county with a similar large city (Reno), and b) all other counties (unexposed). There were no statistically significant period-prevalence rate differences using the two comparison county categories, however, the differences between the comparison county groups themselves were quite large, indicating that either important confounding risk factors were not controlled or estimates were unstable due to the small numbers of cases in the comparison counties. Age, gender, ethnicity, iodine intake and other important risk factors were unavailable in this database and there could have been differential under- or over-diagnosis in this Medicaid population. Interestingly, when comparing the two counties with large urban centers and restricting focus to the 6 (out of 8) more prevalent outcomes (total n=3069), all 6 showed elevated (but not individually significant) rate ratios for the exposed county, ranging 1.01 to 1.89 [Table 3]. While these findings appear to rule out a large perchlorate-related excess (i.e., greater than two-fold) for some thyroid disorders (appearing as routine medical insurance claims), the study did

not have the statistical power to detect a 50% excess for several specific thyroid disorders. Unfortunately, owing to potentially overwhelming confounding, little else can be concluded from this study.

A study of school children in three Chilean cities permitted comparisons on effects of drinking water with widely varying perchlorate content: 0, 5, 100 μg/L.[5] Controlling for age, gender and urinary iodine, a highly significant trend of *increasing* T_4 levels was observed with increasing perchlorate content (which is opposite to the direction expected with perchlorate). The city with the highest concentrations (100 μg/L) had a significant five-fold excess in family history of thyroid-related problems. Children in all three cities had elevated goiter prevalence but it was highest in the city with intermediate concentrations (5 μg/L) which was believed to have iodine deficiencies. A variable introduction of iodized salt in earlier years may have affected these observations. It is not known what role boiling drinking water may have played or how the microbiological quality of drinking water varied across the cities studied. Ethnic and socioeconomic attributes were thought to be similar across the three groups of children but were not controlled for in the analysis. Whether ambient indoor and outdoor temperatures may have played a role in thyroid functional status was not investigated. Uncontrolled confounding, particularly from other environmental factors, make it difficult to interpret the observed effects of drinking water contaminated with perchlorate at levels as low as 5 μg/L on thyroid function.

Lawrence et al. performed a short-term pharmacological study with nine human volunteers[6] over a 4 wk period. The subjects consumed 10 mg/day potassium perchlorate in water for two weeks and were followed for an additional two weeks. There were no changes in T_4 or TSH levels during or after dosing but there was a statistically significant drop in iodide uptake by 40% after two weeks and a rebound to greater than baseline at two weeks following cessation of dosing [Fig. 1]. There was a corresponding increase in urinary iodide excretion during dosing followed by a drop below baseline during rebound. T_3 levels were observed to rise throughout the 28-day trial (trend not tested) [Table 1]. A subsequent study using 8 volunteers and a smaller dose – 3 mg/day – again observed reduced iodide uptake (10% at 2 wks) followed by a rebound to 22% above baseline.[7] These studies imply that iodine depletion is occurring but did not investigate the long term effects of perchlorate at these or lower doses.

The few population-based studies offer little guidance beyond indicating that clinical thyroid disease is not greatly increased in populations with sustained perchlorate-drinking water contamination as high as 15 μg/L. No epidemiological studies have evaluated neurodevelopmental or other deficits in children or adults resulting from perturbed thyroid function over sustained periods of exposure.

3. Neonate Studies

Six studies involved neonatal endocrine evaluations in populations with perchlorate contaminated drinking water.[5,8-12] In each study, the critical covariates were captured with varying degrees of success. Only one of the studies offers a convincing description of neonatal perchlorate effects.

Lamm et al.[8] examined rates of congenital hypothyroidism in 7 counties of California and Nevada with perchlorate contaminated drinking water. This outcome is defined as a result of a mandatory screening program at birth that involves a preliminary T_4 determination followed by a TSH assay in a prescribed subset with low T_4. Age at screen is not considered in this procedure for selecting candidates for TSH determination and screening age distributions by county were not reported. County-specific levels of perchlorate contamination were unavailable. Rates were adjusted only for Hispanic ethnicity, a known risk factor. The county rate ratios for congenital hypothyroidism ranged 0.6 to 1.1 relative to the statewide expected rates and were not statistically significant. Expected rates based on the non-exposed counties of the two states were not used. Most critically lacking in the analysis was classification on age at time of blood sample for the screening test; birth weight, further detail on ethnicity and risk factors were also unavailable. Therefore, there it is likely that uncontrolled confounding has played a role in this study, making it difficult to interpret and allowing for some role for perchlorate in the almost two-fold observed variation in risk of neonatal hypothyroidism across counties.

Li et al.[9] compared T_4 derived from mandatory screening of all newborns in Las Vegas (exposed) and Reno (unexposed) controlling for birth weight (within the restricted range 2.5-4.5 kg), and for age at sample: days 1, 2 or 3 vs. 4. A highly significant period or seasonal effect was observed for both cities (perhaps suggesting an ambient temperature effect) but no difference was observed between cities during the period of exposure (9 out of the 15 months of observation, due to seasonal fluctuation in perchlorate content of drinking water). Highly significant age effects were observed but the dependence of these age effects on exposure (i.e., an exposure interaction) was not examined. For reasons that are obscure, T_4 levels reported in this study were considerably higher than those reported by others (17 vs. 7-10 μg/dL). The restriction on birth weight would be inappropriate if birth weight were an intervening variable, i.e., itself affected by thyroid changes resulting from perchlorate exposure. Regressions on first trimester and 9-month cumulative exposures using monthly perchlorate levels and grouping birth outcomes by month in Las Vegas and Reno revealed no trends for the T_4 difference between the two cities, although more powerful analyses could have been performed using individual observations. This study suggests that large neonatal T_4 differences (compared to usual variability) have not resulted from perchlorate exposures although the possibility of important variation with exposure conditional on neonatal age was not examined.

In a parallel study design Li et al. studied TSH in Las Vegas and Reno births over an eleven-month period.[10] TSH levels were determined on screening samples that were below the 10th percentile on T_4 in each daily batch of samples collected throughout the state, selected without regard to age at screening. TSH levels from the two cities for birth weights restricted to 2.5-4.5 kg were compared adjusting for gender and age at screen (days 2-7 vs. 8-30). Births whose screening sample was taken on the first day were excluded because those TSH levels were considered "unstable." The study did not report whether the age at screen distribution differed between the two cities. Using a log transformed TSH level to facilitate statistical testing, they found no difference in TSH levels between the two populations (a very small *negative* effect was estimated for TSH with exposure) although the log transformation may have suppressed important differences at the high end of the TSH distribution. Examination of an exposure – age interaction was not reported. Excluding births screened on the first day further may have obscured differences arising from perchlorate exposure, differences that pertain to thyroid responsiveness. This study suggests that TSH levels in newborns after the first day did not differ substantially between the cities with and without perchlorate contamination of drinking water.

Brechner et al. studied TSH in Arizona newborns over a three yr period comparing two smaller cities (Flagstaff, Yuma) one of which had perchlorate-contaminated drinking water (Yuma).[11] Controlling for age at screen (days 0, 1-4, 5+) and Hispanic ethnicity, the investigators found a statistically significant elevation in TSH for the exposed population (crude TSH: 19.9 vs. 13.4; adjusted TSH effect not reported). However, the age-at-screening distributions differed considerably between these two cities presenting a possibility for some residual confounding on age. In Yuma (exposed) 5.9% of newborns were screened in the first 24 hours, when TSH levels peak (mean TSH=30), compared with 2.4% of Flagstaff newborns (mean TSH=23). Also, because of the (negative) association of age and exposure, the analysis of variance procedure employed had the potential for bias arising from colinearity. The age and exposure effect estimates would be jointly affected: overestimating exposure and underestimating age effects, or, visa versa. Other factors not controlled included gender and birth weight. This study offers positive support for an association of increased neonatal TSH with perchlorate exposures but, like other studies on this question, it has some unresolved methodological issues.

There is a subtle form of bias in the Brechner and other studies where TSH was determined on a low -T_4 percentile subset of all births that mixes on a daily basis ages at screen for samples from all over the state. Bloods with low T_4 are selected, but the T_4 distribution depends on age. Births with screen ages that usually have higher T_4 (typically after 24 hr) are less likely to be selected for TSH determination and conversely, at ages under 24 hr, births are more likely to be selected. Age-specific TSH comparisons should be unbiased with respect to exposure effects but the TSH estimates themselves will be biased because they represent summary measures of TSH for percentiles of T_4 distributions that differ

with age. The effect of this bias on estimation of overall perchlorate exposure effects is difficult to predict, depending in part on how exposure affects T_4 as well as TSH and how sampling age varied with exposure status. It is conceivable that this bias could explain some of the elevated TSH in perchlorate-exposed neonates of Brechner et al.[11] but the same sampling bias was potentially present in the Li et al. study that found no effect.[10]

Newborns in the study of three Chilean cities revealed a statistically significant decline in TSH (log-transformed) with increasing city-perchlorate levels, a trend opposite to that hypothesized.[5] The analysis was adjusted for gender and age at screening but covariates lacking included iodine intake (known to be low in one city), ethnicity, and birth weight. Important other environmental factors may have played a role such as ambient temperatures, caloric intake and social class. This paradoxical finding parallels the similar result in school age children in the Chilean population (discussed above).

Schwartz analyzed both T_4 and TSH for all California births screened in 1996 making use of detailed covariate information on age, birth weight, ethnicity and birth multiplicity.[12] Perchlorate exposure was assigned using the mother's postal zip code and state water testing data and was ultimately collapsed into four exposure categories: 0, 1-2, 3-12, 13+ μg/L. An analysis of covariance model controlling for age at screening (6 hr increments up to 48 hrs), gender, single vs. multiple birth, birth weight (in 5 levels), and ethnicity (20 categories) produced a highly statistically significant declining trend for T_4 with perchlorate level (0, -9.7,-11.2, -18.2). T_4 in this model declined with age (relative to its final level after 48 hrs) until about 18 hrs (-50 mg/dL below final) and then increased over the next 30 hrs (to 36 mg/dL above final) before assuming its final level after 48 hrs [Table 4]. For TSH (log transformed) there was a significant increasing trend with perchlorate exposure (0, .029, .03, .128), and the TSH level followed a more rapid time course increasing immediately after birth and then declining to final level by 24 hrs [Table 5]. Substantial birth weight, gender, ethnicity and birth multiplicity effects were observed for T_4, and smaller effects for TSH. The models specified in this study tested for uniform additive exposure effects for T_4 and TSH across all covariate categories, including baseline shifts. Another issue of considerable physiological interest would have been whether the amplitudes of the T_4 and TSH surges depended on perchlorate exposure with baseline levels relatively unaffected, which could be tested, for example, with interactions between age and exposure. This study also modeled screening performance - a) "presumptive positive criterion", and, b) a positive finding of congenital hypothyroidism - on the same set of predictors. Not surprisingly, these models did not predict well the standard screening outcomes because the screening algorithm does not take into account the several very important predictors identified in this study. Rather it is based entirely on T_4 without regard to age at screen, birth weight etc. (presumptive positive) and, similarly, on T_4 –based sampling and subsequent TSH determination (>25 μU/ml was interpreted as congenital hypothyroidism). The Schwartz study is by far the most convincing of

the neonatal studies, being based on the most elaborate exposure assignment and the most detailed collection of covariate information pertaining to neonatal thyroid function.

Of the four studies investigating TSH in newborns (Lamm et al.[8], Li et al.,[10] Brechner et al.[11] and Schwartz[12]), Brechner et al.[11] had a somewhat better exposure classification owing to a more narrow, but still ecological, geographical focus (two small cities), and Schwartz had a relatively detailed exposure classification down to the level of zip codes. Only these two studies had positive findings in newborns. The restriction of birth weight in Li et al.[10] could have reduced study sensitivity if thyroid endpoints in non-normal birth weights are especially effected by perchlorate. The strong dependence of thyroid endpoints on birth weight observed in several studies raises the possibility that birth weight itself could be an intervening variable in perchlorate effects. That is, perchlorate exposure may affect birth weight. This would be a testable hypothesis in several of the studies. If birth weight were an intervening variable, birth weight restriction[9,10] or control as a confounder,[9-12] may have resulted in underestimation of exposure effects.

In the one study (Brechner) that reported age-specific perchlorate exposure effects on TSH,[11] the largest effect was in the first 24 hours after birth. This observed exposure – age interaction was not statistically evaluated. The study (Schwartz) with the strongest findings[12] actually focused only on the first 2 days after birth. Therefore excluding day-one screened births as in Li et al.,[10] may well have severely reduced or eliminated the ability of that study to detect a perchlorate effect.

The well-known TSH surge at birth is thought to represent a response to temperature change.[12] This suggests that ambient temperatures – prenatal and perinatal – might be important determinants of thyroid endpoints. The strong period/seasonal effect observed in one study[9] supports this temperature conjecture and the unexpected trends across Chilean cities[5] and variations across U.S. counties[8,12] could also be related to temperature.

Conclusions

To varying degrees, all of the studies in this review examined endpoints that may be insensitive to the consequences of altered thyroid function. No detailed models of thyroid dynamic response were postulated and then endpoints analyzed that would reliably detect specific environmentally induced defects. Nonetheless, one study examining neonatal thyroid status in the first five days found a perchlorate effect that was greatest in the first 24 hours and that rapidly

declined over the next two days, suggesting alteration of thyroid response to the birth event. The issue of iodine depletion in exposed populations was not directly evaluated although experimental evidence of short-term depletion in adults at high doses was observed.

All of the observational field studies utilized "ecological" exposure rather than individual-specific dose measurements; the relative specificity varied widely from "exposed, not exposed," to average, within zip code, concentrations in drinking water. The occupational studies used air sampling to estimate homogeneous exposure groups. Nevertheless, there was evidence of perchlorate effects on neonatal thyroid status, with the studies by Brechner et al.[11] and Schwartz[12] contributing the most compelling observations, and iodine depletion was observed experimentally. The presence of exposure misclassification and potentially serious confounding in many of the studies makes interpretation difficult and allows for the possibility of missed effects even at the level of current thyroid function (e.g. steady state levels of TSH or T_4). The full implications of these findings are unclear but they should be taken seriously, especially in populations already at risk for thyroid deficiency.

The present review differs from a recent summary co-authored by two major participants in industry-funded perchlorate research.[13] That review argues that there is now sufficient evidence to recommend safe levels for regulatory purposes. The authors see no immediate need for refinement of the physiological issues underlying the existing epidemiologic study designs or for new initiatives in evaluating such issues in human populations. Not considered were 1) short term effects of variable exposure during pregnancy, 2) the effects of iodine depletion on the T_4 or TSH surge response at birth, 3) the equilibration of this system under chronic exposure and the masking of potential deficiency states, and 4) the special situation of populations or individuals with inadequate iodine intake.

It is quite clear from the available neonatal studies that screening based on T_4 without regard to age, ethnicity, gender (and possibly birth multiplicity) will not result in optimum screen operating characteristics for the general population aside from possible special features of environmental exposures. Some newborn are being inappropriately evaluated for thyroid deficiency while others needing evaluation are being missed.

References

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National Institute for Occupational Safety and Health - Education and Information Division - Risk Evaluation Branch
Robert M. Park - November 2, 2001

Perchlorate Health Effects

I – iodine P – perchlorate AP – ammonium perchlorate exp – exposure thy – thyroid liv – liver hematol – hematologic fcn – function ITR – interaction outc – outcomes
BL – baseline SD – standard deviation [Tn] – table in paper [Fn] – figure in paper

	Publication	Study Population	ClO_4^- Source and Levels	Dur	Outcomes studied	Findings	Problems/Comment
1	Gibbs JP, Ahmad R, Crump KS, et al JOEM 1998; 40:1072-1082. *Evaluation of a population with occupational exposure to airborne ammonium perchlorate for possible acute or chronic effects on thyroid function.*	Kerr-McGee workers in voluntary med surveil. 1994-98; out of 254, 170 did survey, 130 did single shift evaluation	Airborne exposure to AP in 8 homog. exp. groups: 0.04-627 $\mu m/m^3$ using closed face cassettes	1 day 1-27 yr.	T_3U, T_4, FTI, TSH, liver, kidney and hematol fcn T_4: 7.5 $\mu g/dL$ TSH: 2.0 $\mu IU/ml$	Indication of increase in TSH over work shift: 2.2 -> 2.5. In workforce, T_4 declines and TSH increases from low to high exposure but also from low exposure to unexposed; see inconsistent TSH trends using two lab groups. For both thy and liv outc, SDs increased in high dose group: for thy and liv fcn, averages for low vs high AP very different but %iles up to 75th are not (T5, 6) => big excursion at high exposure end.	Possibly half of eligibles did not participate in shift study; possibly confounded by shift duration - didn't do ITR. Suggestion of inappro. unexposed comparison group. In this steady state and cross-sectional population, difficult to assess thyroid regulatory status. SDs suggest heterogeneity of effect. **Indications of chronic effects.**
2	Lamm SH, Braverman LE, Li FX, et al. JOEM 1999; 41:248-260. *Thyroid health status of ammonium perchlorate workers: a cross-sectional occupational health study.*	American Pacific workers: 37 AP and 21 azide workers: full feasible participation; all from same site with same other work attributes	Airborne exposure in 3 AP groups based on visible dust level; total and respirable AP by individual closed-face samplers 10-11 hrs on subset from ea exp group; levels: (total, mg/day) .01,.34,6.57,59.4; (resp): .02,.09,.60,8.6	1 day n=58; 6 days n=2	Urine AP, T_3, T_4, FTI, TSH, THBR, and hematologic fcn T_4: 7.0 $\mu g/dL$ TSH: 2.6 $\mu IU/ml$	18% of total airborne AP is respirable (range 8-25); urinary excretion of P shows much higher absorbed dose in unexposed workers than expected from air samples: (mg): .88,4.0,10.9,33.6 (assuming 8 hr halflife). Thy, hematol by current exp group: no assoc [T3,4]; absorb dose greatly exceeds resp and total inhaled dose [F5]. See aberrant clearance in 1 of 2 6-day subjects [F2]. Authors conclude no AP health effects.	Some misclassification apparent among exposure groups based on absorbed dose; non inhalable contribution may constitute important deficit in air sampling results. Steady state, cross-sectional population difficult to interpret. **Thy, hematol results based on current, non cumulative AP exposure are uninterpretable for chronic effects.** Possible increasing trend for max(T_3) with exp group.
3	Lawrence JE, Lamm SH, Braverman LE. J Endocrinol Invest 1999; 22:405-407. *The use of perchlorate for the prevention of thyrotoxicosis in patients given iodine rich contrast agents.*	Radiocontrast patient series	Therapeutic high oral doses (1000 mg) in day prior to contrast agent	1 day	Misc. thyroid parameters -	Recommend in high risk patients (low iodide areas and elderly) a combination of perchlorate and contrast agent.	Not relevant to and uninformative on chronic exposure effects in adults and acute effects in infants.

	Publication	Study Population	ClO_4^- Source and Levels	Dur	Outcomes studied	Findings	Problems/Comment
4	Li FX, Squartsoff L, Lamm SH. JOEM 2001; 43:630-634, *Prevalence of thyroid diseases in Nevada counties with respect to perchlorate in drinking water.*	Medicaid population at risk for thyroid disease in Nevada in 1997-98.	Industrial P in drinking water in one county (P = 8.9-11.6 μg/L) vs all others	Lifetime	ICD 240-246; ICD 193: thy cancer	Exposed county (Clark) with Las Vegas compared to the other county with a city (Washoe: Reno) as well as with all other counties. No significant excesses found for exposed county for the 8 outcomes studied. Actually, the comparison counties (one with a city, and all others) for most outcomes differed more between them than with the exposed county. For the 6 more prevalent outcomes (n=3069) the exposed county had higher rates than the unexposed (Washoe) county.	Based on period-prevalence rates. Two outcomes with small numbers are not informative: congenital hypothyroidism (n=22) and thyroid cancer (n=44). **The difference in the comparison counties suggests that uncontrolled confounders or uncertain estimates are affecting this analysis and that the study is uninterpretable for all but large effects.** Confounders might include age, gender, body mass, diet, iodine intake, ethnicity, occupational exposures.
5	Crump C, Michaud P, Tellez R et al. and Crump KS, Gibbs JP. JOEM 2000; 42:603-612. *Does perchlorate in drinking water affect thyroid function in newborns or school-age children?*	School children from 1 or 2 schools in three cities in Chile (n=53,49,60 in 0, low and high P cities); all newborns 2/96-1/99 in same cities (n=8888,468,428)	Geological Na-P in drinking water (city averages: 0, 5.5, 111.6 μg/L)	Recent and lifetime for 6-8 yr-olds; gestation	T_3, T_4, free T_4, FTI, TSH, hematol, liver, kidney, prev:goiter, prev:family h_x thy disease T_4:10.0 μg/dL TSH: 3.0 μIU/mL	Did comparisons across cities. Urinary I/creatine low in city-2 lifetime residents: (1096,862,963); goiter high in city-2 recent residents: (17.0.26.5,23.3%) and high in city-3 lifetime residents: (22.2,19.5,26.0 based on 8,8,13 cases); family h_x of thy disease high in city 3: OR=4.9, (11.1,9.8,30.0); highly signif. increase in T_4 with incr P (1.25,1.34,1,50). Highly signif. decrease in log(TSH+1) in newborns in city-3 – high P (.91,.91,.66) [T9], which is in the unexpected direction. There was a diverse age-at-screen distribution across cities.	Dietary, ethnic, birthwt, SES confounders of thy fcn uncontrolled; observe trends in unexpected directions; suggesting confounding. Unknown if some Chileans boil drinking water. **Significant paradoxical effects indicate uncontrolled confounding and possibly inappropriate thy fcn model in relation to P in this population.** Possible role of ambient temperatures.
6	Lawrence JE, Lamm SH, Pino S, Richman K, Braverman LE. Thyroid 2000; 10:659-663. *The effect of short-term low-dose perchlorate on various aspects of thyroid function.*	9 healthy , male volunteers	K-perchlorate – 10mg/da	14 days	T_3, T_4, FTI, TSH, THBR, RAIU, liver, hematol T_4: 7.0 μg/dL TSH: 1.0 μIU/mL	Assumed identical P doses. Upward trend for T_3 at BL, 7 da, 14da and 28 da. (136,140,151,157; trend not tested). See depressed I-uptake at 14 days (40%) with rebound at 28 days; non-24 hr urinary- and serum-I was unchanged throughout. Authors conclude: no thyroid impact because of large I-storage.	Hematol, liver test results clinically "normal" but no data presented. **Inappropriate assessment: clinical rather than epidemiological.** T_3 effect not addressed; dietary I not controlled or reported. **Suggests long term iodine depletion.**

	Publication	Study Population	ClO_4^- Source and Levels	Dur	Outcomes studied	Findings	Problems/Comment
7	Lawrence JE, Lamm S, Braverman LE. Thyroid 2001. 11:295 (letter) *Low dose perchlorate (3 mg daily) and thyroid function.*	8 healthy, male volunteers	K-perchlorate – 3 mg/da	14 days	T_3, T_4, FTI, TSH, THBR, RAIU, liver, hematol	No signif. changes (data not presented) except for depressed I-uptake at 14 days (10%) with signif. rebound (22%) at 28 days;	**Implies some I depletion over 2 weeks at 3 mg/day** (seen by other investigators at 1.4 mg/day).
8	Lamm SH, Doemland M. JOEM 1999; 41:409-411. *Has perchlorate in drinking water increased the rate of congenital hypothyroidism?*	Newborns in CA and NV in 1996-97 in 7 counties	Industrial perchlorate in drinking water: 4-16 μg/L	gestation	Congenital hypothyroid-ism based on neonatal screen (expected=35/10^5)	Compared counties. Hispanic-adjusted prevalence ratios by county: 0.6 (n=8) to 1.1 (n=136); none statistically significant.	No county-specific levels of P; no individual consumption. Should have used other CA and NV counties for expected rates. **Identification of cases is limited by screening procedure that does not consider age at screen, ethnicity or birthweight.** Unable to address transient developmental sequelae.
9	Li Z, Li FX, Byrd D, et al. and Lamm. JOEM 2000; 42:200-205. *Neonatal thyroxine level and perchlorate in drinking water.*	Newborns in Reno and Las Vegas NV 4/98 – 6/99 with birthwt 2.5-4.5kg and age at screen < 5 days and non ICU	Industrial perchlorate in drinking water of Las Vegas: 0 up to 15 μg/L , measured monthly	gestation	T_4 T_4:17.0 μg/dL	Compared cities. Significant period effect (seasonal) (ΔT_4=.60) when adj for birthwt (.85/kg), age at screen (day 1,2,3 vs 4: -1.275,.408, .758) and gender (.727). No city * period interaction => no P effect. Age * exposure interaction not investigated. Did regressions on monthly means (T_4, cum.P); also, used 10%ile T_4 as an outcome – no effect. See jump in T_4 at newborn return visits in days 2-4.	**These T_4 levels are much higher than in other neonate studies (7-10).** Birthweight may be intervening variable: P causing reduced birthwt via impaired thy fcn. Loss of power in regressions using monthly means instead of individual obs. Early return visits have selection bias: reason for early return.
10	Li FX, Byrd DM, Deyhle GM et al. and Lamm. Teratology 2000; 62:429-431. *Neonatal thyroid-stimulating hormone level and perchlorate in drinking water.*	Newborns in Reno and Las Vegas NV 12/98 – 10/99 with birthwt 2.5-4.5 kg	Industrial perchlorate in drinking water of Las Vegas: 0 up to 15 μg/L , measured monthly	gestation	TSH TSH: 10.0 μIU/mL	Compared cities. TSH levels, adjusted for gender and age at screen (2-7 vs 8-30): no difference for Las Vegas vs Reno	TSH log transformation for variance stabilization could suppress TSH differences in the high range; inadequate control for age at screen (LV vs Reno), ethnicity and birthwt (2.5-4.5 kg); birthwt may be intervening variable. TSH levels may not be relevant vs T_4. **Insensitive to developmental issues and short-term time variability of P exposure.**

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11	Brechner RJ, Parkhurst GD, Humble WO et al. JOEM 2000; 42:777-782. *Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona.*	Newborns 10/94-12/97 in two small Arizona cities whose T_4 screen was below statewide daily 10%ile	Industrial P in drinking water <16 μg/L	gestation	TSH TSH: 13.4 μIU/mL	Compared cities. TSH higher in newborns from exposed city (median: 19.9 vs 13.4); age at screen distribution very different between two cities: exposed screened sooner. Stratifying on age at screen (0, 1-4, 5+ days) and Hispanicity, see signif. increase (p=.017); adj effect not reported.	[TSH levels (13-20) higher than reported for other newborns (7-10).] Selection on T_4 level is problematic due to strong age dependence of T_4 surge at birth thus causing variable %ile discrimination with age (8-40% were screened depending on age). **This effect could increase TSH of the exposed city relative to unexposed city but the effect of the bias is difficult to predict.** Uncontrolled other confounding e.g. birthwt, gest. age, iodine intake, SES.
12	Schwartz J.Dissertation, UC Berkeley, 2001. *Gestational exposure to perchlorate is associated with measures of decreased thyroid function in a population of California neonates.*	99% of California newborns screened for thy disease in 1996	Industrial P in drinking water assigned by zip code: 1-2,3-12,13+ μg/L and then classified in 3 levels	gestation	T_4, TSH, presumptive positive; congenital hypothyroidm T_4: 160 mg/dL TSH: 7.6 μIU/mL	Compared across four levels of estimated exposure. Has detailed covariates: birthwt, age at screen in hours, ethnicity in 20 groups; birth multiplicity; ancova model with extrensive control of most confounders finds highly significant decrease in T_4 (mean=166) with P level (0,-9.7,-11.2,-18.2) and large effects for birthwt (-72 for bw 1500-2500), age (-50 for hours 7-18) and ethnic gps (-10 to -30); see initial T_4 fall followed by surge by 12 hr. and stays elevated until 36 hr.; initial onset of TSH surge unresolvable in time; stays elevated till 18 hr. Signif. P effect on TSH (0,.029,.03, .128) but birthwt effects modest (-.09 for <1.5kg). Model for presumptive positives shows strong age at screen and ethnicity effects; for cong hypothyroidism, insignif. effect.	[T_4 is reported at levels 10,000 fold higher than in other studies.] Presumptive positive criterion not clear (all at or below 9mg/dl plus lowest 5% immediately above 9mg/dl?). No P-ITR reported, e.g. P * age (esp on surge amplitude), P * birthwt; possible selection bias in identification of TSH subjects; Age at screen was not included in logistic regression model of congenital hypothyroidemia. **This study presents strong evidence of perchlorate health effects in neonates from drinking water contamination with perchlorate.**

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13	Soldin OP, Braverman LE, Lamm SH. Therapeutic Drug Monitoring 2001; 23:316-331. *Perchlorate clinical pharmacology and human health: a review.*	Review of animal and human evidence.				This review, co-authored by two major participants in industry funded perchlorate research, argues that there is now sufficient evidence to recommend safe levels for regulatory purposes, i.e., at this time there is no immediate need for further refinement of the physiological issues underlying the existing epidemiologic study designs or for new initiatives in evaluating perchlorate issues in human populations.	Not considered in this review are issues such as 1) short term effects of variable exposure during pregnancy, 2) the effects of maternal iodine depletion on T_4 or TSH surge response at birth, 3) the equilibration of this system under chronic exposure and the masking of potential deficiency states, and 4) the special situation of populations with inadequate iodine intake.